REBUTTAL TO THE PI COMMITTEE IN THE W.R. GRACE BANKRUPTCY PROCEEDING

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INTRODUCTION

My name is Samuel P. Hammar, M.D., and I am board certified in anatomic and clinical pathology. My area of expertise is pulmonary pathology and my primary area of interest is that of asbestos-related diseases such as mesothelioma. I previously submitted my report on asbestos-induced lung and pleural disease on behalf of the W.R. Grace Asbestos Claimants Committee on September 13, 2006. I have been asked by Caplin and Drysdale to review the expert witness reports submitted from Grace's experts and to rebut/comment on their statements.

Rebuttal to Dr. Grover M. Hutchins' report dated 10/3/06:
With respect to Dr. Grover M. Hutchins' expert report, the cases he cites would and could be further evaluated to determine if they are or are not mesothelioma. Group 2 of his cases (#24, #25 and #26) could potentially be mesotheliomas in that solitary pulmonary nodules have been the identifying pathologic finding in some cases of mesothelioma. In case #25, in which the chest wall mass was stated to have been an adenocarcinoma and not a mesothelioma, this could be further evaluated to determine if, in fact, that was correct. Obviously, mesotheliomas can present as chest wall masses. Case #26 was a case I reviewed, which was not mesothelioma but was a pseudomesotheliomatous adenocarcinoma, which presents with features that are essentially identical to mesothelioma. In Group 3 of the cases (#27-40), all these cases should be reviewed to further determine if they were or were not mesotheliomas.

Rebuttal to Dr. Suresh Moolgavkar's reports:
With respect to Dr. Suresh Moolgavkar's report stating there is no threshold below which exposure to asbestos in an occupational or bystander setting cannot cause mesothelioma, I suggest Dr. Moolgavkar review the articles by: 1) Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 2000;44:565-601; 2) Iwatsubo Y, Pairon JC, Boutin C, et al. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. Am J Epidemiol 1998;148:133-142; 3) Rödelsperger K, Jöckel, KH, Pohlabein H, et al. Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study. Am J Ind Med 2001;39:262-275; 4) Rolland P, Ducamp S, Gramond C, et al. Risk of pleural mesothelioma: A French population-based case-control study (1998-2002). Lung Cancer 2006;54:S9(35); and 5) Hillerdal G. Mesothelioma: cases associated with non-occupational and low dose exposures. Occup Environ Med 1999;56:506-513. The fact Dr. Moolgavkar disagrees doesn't necessarily mean he is right and other experts are wrong. If one wants to protect individuals from diseases such as mesothelioma, one has to make sure those individuals who are exposed to asbestos are exposed at the lowest levels possible in order to prevent the occurrence of such asbestos-related diseases.

Even in those individuals who have been exposed to very high concentrations of asbestos, such as asbestos insulators or asbestos miners and millers who have very high concentrations of asbestos in their lung and pleural tissue, only a relatively small

percentage of those individuals (1-10%) develop mesothelioma. This suggests there is individual susceptibility to asbestos exposure. This may also explain the significant number of mesothelioma cases where there is low level exposure to asbestos. In addition, even in those individuals who develop mesothelioma and have high concentrations of asbestos in their lungs or pleura, there is no published data stating how much of the total dose of asbestos they were exposed to it took to cause their mesothelioma or, for that matter, any asbestos-induced disease.

With respect to Dr. Moolgavkar's statement that he doesn't believe every exposure to asbestos a person has contributes to the development of a disease such as mesothelioma, I would say that no one can prove it does not. No one knows the exact molecular changes that occur at what point in time to be able to eliminate a certain exposure to asbestos that a person had.

With respect to the statement by Dr. Moolgavkar concerning other causes of mesothelioma, the only causes that have currently been recognized for certain in the United States are asbestos and therapeutic radiation. The total number of therapeutic radiation cases that have been reported are about 60 (Hammar SP, Henderson DW, Klebe S, Dodson RF. Neoplasms of the pleura. In: Dail DH, Hammar SP (Eds). Pulmonary Pathology, 3rd Edition. New York: Springer-Verlag. In press). The cases cited by Peterson et al. as potential causes of mesothelioma have not withstood further evaluation. There are cases of mesothelioma in which a definitive cause cannot be determined.

With respect to Dr. Moolgavkar's statement concerning Dr. Frank's claim that pericardial and testicular mesotheliomas are caused by asbestos cannot be proven because of lack of epidemiologic studies, I would inform Dr. Moolgavkar that there have been plenty of examples of tumors of the tunica vaginalis that have been found in persons who have been exposed to asbestos. The same is true for pericardial mesothelioma, such as the report by Dr. Churg et al. in which talc containing asbestos was used to obliterate a pericardial effusion and the individual developed mesothelioma approximately fifteen years later. With respect to Dr. Moolgavkar's claim that it is hard to envisage how asbestos fibers could reach the testes, I would refer him to anatomy books concerning lymphatics. As Dr. Dodson and I have shown, asbestos is translocated from the lungs into the abdominal cavity and there is no reason why asbestos could not reach the tunica vaginalis (Dodson RF, O'Sullivan MF, Huang J, Holiday DB, Hammar SP. Asbestos in extrapulmonary sites: omentum and mesentery. Chest 2000; 117(2):486-493). Also, the article by Heller et al. clearly shows that asbestos can reach ovarian tissue in women at very high concentrations (Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. Am J Ind Med 1996;29:435-439).

Dr. Moolgavkar stated that crocidolite and amosite are many times more potent than chrysotile in causing mesothelioma and that's because of biopersistence of the fibers. If one assumes the carcinogen has to reach the site where the tumor began (pleura or pericardium), then the studies by Suzuki and Yuen, Dodson et al., and Sebastian et al.,

clearly show that the most common fiber one finds in the pleura of people who develop mesothelioma is chrysotile.

There is extensive evidence that chrysotile causes mesothelioma. One only needs to review the following articles:

- Yano E, Wang Z-M, Wang X-R, Wang, M-X, Lan Y-J. Cancer mortality among workers exposed to amphibole-free chrysotile asbestos. Am J Epidemiol 2001;154:538-543.
- Camus M, Siemiatycki J, Meek B. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. N Eng J Med 1998;338:1565-1571.
- Piolatto G, Negri E, La Vecchia C, et al. An update of cancer mortality among chrysotile asbestos miners in Balangero, northern Italy. Br J Ind Med 1990;47:810-814.
- Cullen MR, Baloyi RS. Chrysotile asbestos and health in Zimbabwe: I. Analysis of miners and millers compensated for asbestos-related diseases since independence (1980). Am J Ind Med 1991;29:163-169.
- Sturm W, Menze B, Krause J, Thriene B. Use of asbestos, health risks and induced occupational diseases in the former East Germany. Toxicol Lett 1994;72:317-324.
- Dell L, Teta MJ. Mortality among workers at a plastics manufacturing and research development facility: 1946-1988. Am J Ind Med 1995;28:373-384.
- Robinson C, Lemen R. Mortality patterns, 1940-1975, among workers employed in an asbestos textile friction and packing products manufacturing facility. In: Dust and Disease, Lemen and Dement (Eds.), Pathotox Publishers 1979.
- Mancuso TF. Relative risk of mesothelioma among railroad machinists exposed to chrysotile. Am J Ind Med 1988;13:639-657.
- Dement JM, Brown DP, Okun A. Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. Am J Ind Med 1994;26:431-447.
- Smith AH, Wright CC. Chrysotile asbestos is the main cause of pleural mesothelioma. Am J Ind Med 1996;30:252-266.
- Helsinki Consensus Report. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. Scan J Work Environ Health 1997;23:311-316.
- Environmental Health Criteria 2003. Chrysotile asbestos. World Health Organization 1998.
- Landrigan PJ, Nicholson WJ, Suzuki Y, Ladou J. The hazards of chrysotile asbestos: a critical review. Industrial Health 1999;37:371-280.
- Landrigan PJ. Asbestos – still a carcinogen. N Eng J Med 1998;338:1618-1619.
- Stayner LT, Dankovic DA, Lemen RA. Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. Am J Public Health 1996;86:179-186.
- Federal Register, June 20, 1986. Occupational Exposure to asbestos, tremolite, anthophyllite and actinolite.
- Federal Register, July 12, 1989. Asbestos: Manufacture, importation, processing, and distribution in commerce prohibitions.
- Federal Register, August 10, 1994. Occupational exposure to asbestos.
- World Health Organization, IARC Monographs September 1979. Chemicals and industrial process associated with cancer in humans.
- NIOSH. Atlas of respiratory disease mortality, United States: 1982-1993. U.S. Department of Health and Human Services, August 1998.
- Report on carcinogens, 9th Edition. U.S. Department of Health and Human Services 2000.

With respect to the claim by Dr. Moolgavkar that there is limited evidence (Mossman and Churg 1998) that amphiboles are more potent than chrysotile in causing asbestosis, I would refer him to the recent article by Hein et al. (Hein MJ, Stayner L, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. Occup Environ Med 2007) in which the authors concluded "this study confirms the findings from previous investigations of excess mortality from lung

cancer and asbestosis and a strong exposure-response relationship between estimated exposure to chrysotile and mortality from lung cancer and asbestosis."

With respect to fiber dimension and cancer risk, there is a great deal of uncertainty with respect to the length at which fibers do not cause injury. There is evidence that longer fibers generally cause more injury than shorter fibers, but even that is variable as is discussed by Dodson et al. (Dodson RF, Atkinson MAL, Levin JL. Asbestos fiber length as related to potential pathogenicity: a critical review. Am J Ind Med 2003;44:291-297). Also, Churg challenged the Stanton hypothesis in 1993 and 1994 when he found the majority of cases of mesothelioma occurred in individuals whose lung tissue contained predominantly amosite asbestos fibers that were shorter than 5 μm long.

With respect to the claims by Dr. Moolgavkar concerning smoking, asbestos and lung cancer, there is overwhelming evidence that asbestos and cigarette smoke act synergistically, usually in a multiplicative synergistic effect, in causing lung cancer (Saracci R. The interaction of tobacco smoking and other agents in cancer etiology. Epidemiol Rev 1987: 9:175-193).

With respect to Dr. Moolgavkar's claim that asbestos causes cancers other than mesothelioma, there is evidence that that is the case, including laryngeal, colon and kidney cancers. These occur primarily in persons who have been exposed to relatively high concentrations of asbestos.

Respectfully submitted

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